Risks of triple negative breast cancer associated with cancer predisposition gene mutations.

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Abstract Text:

Background: Multigene panel testing for hereditary cancer includes genes identified as hereditary breast and/or ovarian cancer (HBOC) genes despite limited data regarding the precise cancer risks associated with mutations in these genes. Here we report on risks of breast cancer and separately risks of triple negative breast cancer associated with mutations in 20 predisposition genes.

Methods: A cohort of 10,091 individuals with breast cancer, including 2,400 with triple negative breast cancer, were tested for mutations with the BreastNext and OvaNext clinical genetic testing panels. A further 2,100 individuals with triple negative breast cancer were tested for the same genes by custom capture-based sequencing. Case-control analyses were performed comparing the frequencies of pathogenic mutations from Caucasian breast cancer cases with frequencies from Caucasian study matched controls, and Caucasian, non-Finnish, non-TCGA controls from the ExAC database.

Results: Pathogenic mutations were identified in 9.6% of the BreastNext and OvaNext breast cancer cases. Mutations in the ATM and CHEK2 genes were associated with moderate risks (OR > 2) and mutations in PALB2 were associated with high-risks (OR > 5) of breast cancer. Pathogenic mutations in MSH6 and RAD51D were associated with moderate risks of breast cancer. Predicted pathogenic missense mutations in CHEK2, MSH2, and MSH6 were associated with moderate risks of breast cancer. In contrast, pathogenic mutations were observed in 13% of 4,500 triple negative breast cancers from the two studies. Mutations in the PALB2, RAD51D, and BARD1 homologous recombination repair (HRR) genes were associated with high risks of triple negative breast cancer, whereas mutations in BRIP1, RAD51C, and NBN were associated with moderate risks.

Conclusions: This large breast and ovarian cancer case-control analysis provides useful data for predisposition genes previously lacking risk estimates, that will be useful for clinical risk management of patients. The study of triple negative breast cancer suggests that several HRR genes, previously excluded as moderate or high risk breast cancer genes, all have higher, clinically relevant risks of triple negative breast cancer.